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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/966,847	09/28/2001	Rina Goldshtein	23908-501	5004

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EXAMINER

LEWIS, PATRICK T

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 01/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,847	GOLDSHTEIN, RINA	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 and 33-49 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 and 33-49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
 a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-18 and 33-49) wherein the lipophilic compound/particle is a vitamin, antibiotic or hormone and wherein the amphiphilic polymer is a natural polysaccharide in Paper No. 8 dated April 11, 2003 is acknowledged.
2. Claims 19-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8 dated April 11, 2003.

Applicant's Response dated September 30, 2003

3. In the Response filed September 30, 2003, claims 1, 3, 11, 14, 38, and 45-46 were amended; claims 19-32 were canceled. Applicant submitted a terminal disclaimer and declaration under 37 CFR 1.132. Applicant presented arguments directed to the rejection of claims 1-18 and 33-49 under 35 U.S.C. 112, first paragraph, as failing to comply with written description and to the rejection of claims 1-7 under 35 U.S.C. 103(a). Claims 1-18 and 33-49 are pending. An action on the merits of claims 1-18 and 33-49 is contained herein below.
4. The provisional double patenting rejection of claims 5, 8-10, 12-18, 43-44, and 46-49 under 35 U.S.C. 101 is maintained for reasons set forth in the Office Action dated June 30, 2003.

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5. The provisional rejection of claims 1-4, 6-7, 11, 33-42, and 45 under the judicially created doctrine of obviousness-type double patenting has been rendered moot in view of the terminal disclaimer filed September 30, 2003.

6. The rejection of claims 1-18 and 33-49 under 35 U.S.C. 112, first paragraph, has been withdrawn in view of applicant's arguments dated September 30, 2003.

7. Applicant's arguments with respect to claims 1-7 under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Objections/Rejections of Record Set For the in Office Action dated June 30, 2003

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Claims 5, 8-10, 12-18, 43-44, and 46-49 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 20-22, 25-27, 29, 31, 32-33, 58-59, 61, 63, 65, and 66 of copending Application No. 10/256,023. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the

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applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Parikh et al. US 6,228,399 (Parikh).

Parikh discloses compositions of sub-micron and micron stable particles of water-insoluble or poorly soluble drugs or other industrially useful insoluble compounds (column 1, lines 5-18). The compositions contain microparticles consisting essentially of a drug, a phospholipid, and at least one surface modifier (Abstract). The term "micro" refers to a particle having diameter of from nanometers to micrometers (column 1, lines 32-46). The surface modifiers/phospholipids generally adsorb to surfaces of drug particles, and convert lipophilic to hydrophilic surfaces with increased stability and possibly modify the zeta potential of surfaces with more charge repulsion stabilization (column 2, lines 20-40). Phospholipid and surface modifier(s) are adsorbed onto the surfaces of drug particles in sufficient quantity to retard drug particle growth, reduce drug average particle size from 5 to 100 μm to sub-micron and micron size particles by one or combination of methods known in the art, such as sonication, homogenization, milling, microfluidization, precipitation or recrystallization or precipitation from supercritical fluid, and maintain sub-micron and micron size particles on subsequent storage as suspensions or solid dosage form. The formulations may be dried, e.g., by lyophilization, fluid or spray drying, into powders, which can be resuspended or filled into capsules or converted into granules or tablets with the addition of binders and other excipients known in the art. Examples of preferred water-insoluble drugs include

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immunosuppressive agents such as cyclosporins, antibiotics, sedatives, hormones, and nutrients (column 2, lines 59-67; column 3, lines 1-46). The phospholipid may be any natural or synthetic phospholipid. Examples of suitable surface modifiers include methylcellulose, hydroxycellulose, hydroxy propylcellulose, polyethylene glycols, and chitosans. Formulations containing microparticles provide some specific advantages over the unformulated non-micronized drug particles (column 1, lines 32-47). The advantages include improved oral bioavailability of drugs that are poorly absorbed from GI tract, development of injectable formulations that are currently available only in oral dosage form, less toxic injectable formulations that are currently prepared with organic solvents, sustained release of intramuscular injectable drugs that are currently administered through daily injection or constant infusion, and preparation of inhaled, ophthalmic formulation of drugs that otherwise could not be formulated for nasal or ocular use.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 8-18 and 33-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rolfes et al. U.S. Patent 6,221,399 (Rolfes) in combination with Parikh et al. U.S. Patent 6,228,399 (Parikh).

Claims 8-18 and 33-49, drawn to a method for forming a hydrophilic inclusion complex comprising forming an emulsion comprising an amphiphilic molecule in an aqueous solvent and lipophilic compounds in a non-aqueous solution, forming nano-sized lipophilic particles in a nano-emulsion, and removing carrier solvent from nano-emulsion. Applicant has elected to have the invention examined wherein the lipophilic particles are vitamins, antibiotics, or hormones and wherein the amphiphilic polymer is a natural polysaccharide.

Rolfes teaches process for making a controlled release product for oral administration from an interpolymer complex and an active agent (column 4, lines 39-67; column 5, lines 1-18). The process comprises: 1) dissolving a first polymer in a solvent therefor, 2) dissolving a second complementary polymer in a solvent therefor, 3) mixing the first polymer solution and the second complementary polymer solution, 4) mixing the combined polymer solution of step 3 with the active agent in the form of a dry powder or in the form of a solution, dispersion, suspension, emulsion or slurry of the active agent in a liquid medium, and 5) spraying the product of step 4 into a vessel to remove at least partially the solvents and thereby to produce solid particles of the

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interpolymer complex. The solvents and liquid medium used may be the same or different (column 9, lines 17-37). Rolfes teaches the use of vitamins and antibiotics as active agents incorporated into the interpolymer complex (column 8, lines 1-4). Polymers used to form the interpolymer complex include guar gum, cellulose and its derivatives, starches and their derivatives, and xanthan gum (column 8, lines 32-64). The complexation occurs via reversible physical molecular forces such as hydrogen bonding, hydrophobic interactions, van der Waals forces, electrostatic- ionic- or Coulomb forces and combinations of these interactions excludes irreversible chemical forces such as covalent bonding (column 6, lines 46-51).

Rolfes differs from the instantly claimed invention in that: 1) Rolfes does not teach active agents as nano-sized; 2) Rolfes does not explicitly teach dissolving the active agent in a non-aqueous solvent; and Rolfes does not describe the apparatus employed in forming the inclusion complex; however, these deficiencies would have been obvious to one of ordinary skill in the art at the time of the invention when viewed in light of Parikh.

Parikh teaches compositions of sub-micron and micron stable particles of water-insoluble or poorly soluble drugs or other industrially useful insoluble compounds (column 1, lines 5-18). The compositions contain microparticles consisting essentially of a drug, a phospholipid, and at least one surface modifier (Abstract). The term "micro" refers to a particle having diameter of from nanometers to micrometers (column 1, lines 32-46). The surface modifiers/phospholipids generally adsorb to surfaces of drug particles, and convert lipophilic to hydrophilic surfaces with increased stability and

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possibly modify the zeta potential of surfaces with more charge repulsion stabilization (column 2, lines 20-40). Phospholipid and surface modifier(s) are adsorbed onto the surfaces of drug particles in sufficient quantity to retard drug particle growth, reduce drug average particle size from 5 to 100 μm to sub-micron and micron size particles by one or combination of methods known in the art, such as sonication, homogenization, milling, microfluidization, precipitation or recrystallization or precipitation from supercritical fluid, and maintain sub-micron and micron size particles on subsequent storage as suspensions or solid dosage form. The formulations may be dried, e.g., by lyophilization, fluid or spray drying, into powders, which can be resuspended or filled into capsules or converted into granules or tablets with the addition of binders and other excipients known in the art. Examples of preferred water-insoluble drugs include immunosuppressive agents such as cyclosporins, antibiotics, sedatives, hormones, and nutrients (column 2, lines 59-67; column 3, lines 1-46). The phospholipid may be any natural or synthetic phospholipid. Examples of suitable surface modifiers include methylcellulose, hydroxycellulose, hydroxy propylcellulose, polyethylene glycols, and chitosans. Formulations containing microparticles provide some specific advantages over the unformulated non-micronized drug particles (column 1, lines 32-47). The advantages include improved oral bioavailability of drugs that are poorly absorbed from GI tract, development of injectable formulations that are currently available only in oral dosage form, less toxic injectable formulations that are currently prepared with organic solvents, sustained release of intramuscular injectable drugs that are currently administered through daily injection or constant infusion, and preparation of inhaled,

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ophthalmic formulation of drugs that otherwise could not be formulated for nasal or ocular use.

It would have been obvious to one of ordinary skill in the art at the time of the invention utilize nano-sized active agents to form the inclusion complex taught by Rolfes. One of ordinary skill in the art would have been motivated to employ formulations of nano-sized particles based on the disclosure of Parikh which teaches specific advantages over the unformulated non-micronized drug particles. One of ordinary skill in the art is seen as one having a PhD in organic chemistry or biochemistry conducting research in the field of host-guest chemistry. Although not specifically taught by Rolfes, it would have been obvious to one of ordinary skill in the art to use a non-aqueous solvent to dissolve drugs that are not water-soluble. The employment of appropriate experimental conditions such as temperature, solvent selection, and drying method are seen to be well within the purview of one of ordinary skill in the art. Although Rolfes does not describe the apparatus for forming the polymer inclusion complex in great detail, Rolfes teaches that the polymer solution and the active agent solution are prepared separately and then mixed. In the absence of some proof of a secondary nature to obviate the instant rejection, or of some specific limitations which would tip the scale of patentability in the favor of the instantly claimed invention, it would have been obvious to one of ordinary skill in this art at the time of the invention to formulate a hydrophilic inclusion complex comprising forming an emulsion comprising an amphiphilic molecule in an aqueous solvent and lipophilic compounds in a non-

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aqueous solution, forming nano-sized lipophilic particles in a nano-emulsion, and removing carrier solvent from nano-emulsion.

Conclusion

15. Claims 1-18 and 33-49 are pending. Claims 1-18 and 33-49 are rejected. No claims are allowed.

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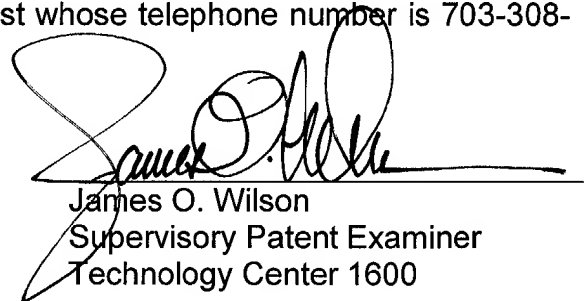
Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD
Examiner
Art Unit 1623



James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

ptl
January 7, 2004